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SUITE 102  
WARRENTON, VA 20186

EXAMINER

MONDESI, ROBERT B

ART UNIT	PAPER NUMBER
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1652

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Office Action Summary</b></p>	<p><b>Application No.</b></p> <p>10/509,307</p>	<p><b>Applicant(s)</b></p> <p>DOI ET AL.</p>	
	<p><b>Examiner</b></p> <p>Robert B. Mondesi</p>	<p><b>Art Unit</b></p> <p>1652</p>	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on April 3, 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-56 is/are pending in the application.
- 4a) Of the above claim(s) 1-13, 15-50 and 52-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14 and 51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 September 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### *Response to restriction requirement*

Applicants' election with traverse of Invention IV, **Claims 14 and 51** and the further election of SEQ ID NO: 1 in amendment, filed April 3, 2007 is acknowledged. The traversal is on the ground(s) that the instant application is a § 371 National Stage entry which takes into consideration the unity requirements for applications entering from the PCT application. Contrary to the Examiner's comments, in the counterpart International application, unity was found with respect to many of the claims, as shown in the International Search Report and Examination Report. Thus, all claims in all of the groups should be examined at this time. With regard to the non-elected claims, it is respectfully submitted that these claims should be examined at this time since there appears to be no serious burden on the part of the Examiner to search the entire scope of the claims. At a minimum, these claims should be rejoined upon the allowability of the subject matter of Group IV due to their relationship to the subject matter of the remaining groups. It is believed that the subject matter has the same concept from the standpoint that the searches would overlap to some extent. Under M.P.E.P. § 803, if there is no serious burden in the examination of all of the claims even if the claims are directed to separate inventions, the Examiner must examine all claims at this time. It would appear that § 803 applies to the current situation and therefore the restriction requirement should be withdrawn and all claims should be examined at this time. At a minimum, the Examiner should re-group these non-elected claims upon the allowability of the Group IV subject matter.

This is not found persuasive because as applicants have correctly stated the instant application is a s a § 371 National Stage entry which takes into consideration the unity requirements for applications entering from the PCT application. The scope and breath of the claims encompass a 5 amino acid fragment of a peptide comprising the amino acid sequence of SEQ ID NO: 1. The mentioned fragment is not a contribution over the prior art as indicated by the 35 U.S.C 102(b) rejection below. Also of important note is the fact that the examiner is currently examining the instant application and is not bound by decisions made by the PCT organization. Furthermore the basis of lake of unity of invention have nothing to do with a lack of search burden. Applicants are making arguments that apply to applications that are restricted under 35 U.S.C 121 and not under the unity of invention standards. However in the interest of full disclosure applicants are informed that :

Therefore the requirement is still deemed proper and is made FINAL. **Claims 1-56** are pending in this application. **Claims 1-13, 15-50 and 52-56** are withdrawn from further consideration because these Claims are drawn to non-elected inventions. **Claims 14 and 51** are currently under examination.

***Priority***

The current application filed on November 19, 2004 is a 371 of PCT/JP03/04120 filed on 03/31/2003, which in turn claims priority to foreign application, JAPAN 2002-095291 filed on 03/29/2002; JAPAN 2002-095390 filed on 03/29/2002; JAPAN 2002-095442 filed on 03/29/2002 JAPAN 2002-095486 filed on 03/29/2002. A certified copy of foreign priority documents has been provided.

***Preliminary Amendment***

The preliminary amendment filed November 11, 2004; October 27, 2004 and September 27, 2004 have been entered.

***Drawings***

Drawings filed September 27, 2004 have been objected to because Fig. 9 contains text in a foreign language (presumably Japanese).

***Information Disclosure Statement***

The IDS filed April 3, 2007 and June 2, 2005 have been received and are signed and considered; a copy of the PTO 1449 is attached to the following document.

***Claim Objection(s)***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 14 and 51** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a peptide comprised of at least 5 consecutive amino acid residues in an amino acid sequence of at least one peptide of BMAL1, BPL1 or SEQ ID NO: 1; a peptide having mutations of one to several amino acid residues in an amino acid sequence of at least one peptide of said BMAL1, BPL1 or SEQ ID NO: 1 and a peptide having a homology of 70% or more to at least one peptide of said BMAL1, BPL1 or SEQ ID NO: 1. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by an unclear functional relationship to BMAL1, BPL1 or SEQ ID NO: 1. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity and the limitation that the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3. The specification does not identify any particular portion of the structure that must be characteristics of the claimed genus are not described. The only adequately described species is BMAL1, BPL1 or SEQ ID NO: 1 and no active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." (See page 1117.) The specification does not it clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116), As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only BMAL1, BPL1 or SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U. S.C. 112, first paragraph. Applicant is reminded that *Vas-cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision.

**Claims 14 and 51** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir.1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art,

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whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1-2 .Breadth of the claims and the nature of the invention..

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method for preventing and/or treating disease(s) caused by the phosphorylation of c-Jun by JNK3, wherein the method comprises utilizing one or more polynucleotides encoding at least one peptide selected from the following peptide group having a function for interacting with c-Jun N-terminal kinase 3 (JNK3) to express the peptide encoded by the polynucleotides, wherein the peptide inhibits the phosphorylation of c-Jun by JNK3: (i) BMAL1, (ii) BPL1, (iii) a peptide

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comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List, (iii) a peptide comprising at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (iv) a peptide comprised of at least 5 consecutive amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (v) a peptide having mutations of one to several amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (vi) a peptide having a homology of 70% or more to at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3.

#### 3-4. The state of prior art and the level of predictability in the art.

The prior art is silent with regards to a method for preventing and/or treating disease(s) caused by the phosphorylation of c-Jun by JNK3, wherein the method comprises utilizing one or more polynucleotides encoding at least one peptide selected from the following peptide group having a function for interacting with c-Jun N-terminal kinase 3 (JNK3) to express the peptide encoded by the polynucleotides, wherein the peptide inhibits the phosphorylation of c-Jun by JNK3: (i) BMAL1, (ii) BPL1, (iii) a peptide comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List, (iii) a peptide comprising at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (iv) a peptide comprised of at least 5 consecutive amino acid residues in an amino acid

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sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (v) a peptide having mutations of one to several amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (vi) a peptide having a homology of 70% or more to at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3.

However the prior art teaches that it has long been known how to mutate proteins, but it has been similarly long been known that such mutations are not reasonably predictive of activity for any particular protein. For example, Rudinger (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7 discusses the peptide hormones and the characteristics of amino acids as components of the peptide hormones (TITLE). (It is noted that Rudinger discusses peptide hormones, but the general areas of unpredictability are common to all proteins.) In doing so, Rudinger notes that many amino acids may be grouped according to general characteristic (pp. 1-3), and many of these are also classified in two or more classifications (p. 3). Hence, simple mutations of "type" are not reasonably predictable, because there are multiple types to any particular amino acid. Moreover, Rudinger finds that the context of any amino acid is important for structure (pp. 3-4), and that therefore, simple deletions, insertions, or substitutions are also not reasonably predictable, because not only is "type" important, but context is also important, having longer-range effects than that of simply type. Further, Rudinger discusses the mechanisms of information transfer (e.g,

binding and effecting a receptor, which is analogous to any protein binding anything and causing any particular effect) (pp. 4-5). In doing so, Rudinger finds that there exist "patterns" on molecules for recognition, which may involve amino acids close by in the amino-acid polypeptide sequence, or far away (Id.). As such the conformation of the whole molecule is important, and any particular amino acid change, deletion, or addition, may alter the conformation of the molecule enough to affect any particular binding and effect on another molecule.

In analyzing the significance of such observations, Rudinger states that:

In a given molecule, some amino acids or sequences obviously owe their 'significance' to their inclusion in the pattern which is directly involved in recognition by, and binding to, the receptor. However, the fact that the existence of this pattern is dependent on a conformation stabilized by intramolecular interactions, ..., implies that other amino acids or sequences contributing to this conformational stability will be no less 'significant' for the biological activity of the molecule.

(p. 5).

And, in conclusion, Rudinger states:

The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study. The careful design of synthetic analogues, and their evaluation in biological systems which permit separate analysis of the various phases of hormone action, is the best way to obtaining such information.

(p. 6).

Bowie, et al. (1990) Science, 247 : 1306-10 provides similar insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discusses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). In general, Bowie continues to reflect the observations of Rudinger: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10).

Hence, the nature of the invention is not reasonably predictable for any of the particular proteins and genes claimed, due to the unpredictability of structure-function relationships.

5. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

6-7. The amount of guidance present and the existence of working examples.

The applicant has not provided any guidance or working with regards to a method for preventing and/or treating disease(s) caused by the phosphorylation of c-

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Jun by JNK3, wherein the method comprises utilizing one or more polynucleotides encoding at least one peptide selected from the following peptide group having a function for interacting with c-Jun N-terminal kinase 3 (JNK3) to express the peptide encoded by the polynucleotides, wherein the peptide inhibits the phosphorylation of c-Jun by JNK3: a peptide comprised of at least 5 consecutive amino acid residues in an amino acid sequence of at least one peptide (i) BMAL1, (ii) BPL1, (iii) a peptide comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List, wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, or a peptide having mutations of one to several amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, or a peptide having a homology of 70% or more to at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3.

On pages 34-48 of the specification of the instant application, applicants have provided some limited guidance in Examples 1-4 with regards to a method of inhibiting the phosphorylation of c-Jun by JNK3 by utilizing (i) BMAL1, (ii) BPL1 or (iii) a peptide comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List.

8. The quantity of experimentation necessary.

The amount of experimentation that is required is undue: while a method of inhibiting the phosphorylation of c-Jun by JNK3 by utilizing (i) BMAL1, (ii) BPL1 or (iii) a peptide comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List might be considered routine, a method of preventing and/or treating

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disease(s) caused by the phosphorylation of c-Jun by JNK3, wherein the method comprises utilizing one or more polynucleotides encoding at least one peptide selected from the following peptide group having a function for interacting with c-Jun N-terminal kinase 3 (JNK3) to express the peptide encoded by the polynucleotides, wherein the peptide inhibits the phosphorylation of c-Jun by JNK3: (i) BMAL1, (ii) BPL1, (iii) a peptide comprised of the amino acid sequence represented by SEQ ID NO:1 in Sequence List, (iii) a peptide comprising at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (iv) a peptide comprised of at least 5 consecutive amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (v) a peptide having mutations of one to several amino acid residues in an amino acid sequence of at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3, (vi) a peptide having a homology of 70% or more to at least one peptide of said (i) to (iii), wherein the peptide has a function for inhibiting the phosphorylation of c-Jun by JNK3 is not routine and requires more experimentation. Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

It must be noted that the issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill

level of the artisan and the guidance presented in the instant specification and the prior art of record. The Applicants make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "... scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Therefore, for the instant specification to be enabling, it needs to provide direction/guidance regarding an acceptable number of different variants used in the method of the invention.

Absent sufficient guidance/direction one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and insufficient working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to test all the different type of nucleic acid and peptide variants encompassed by the claimed invention would constitute undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a

manner that reasonably correlates with the scope of the claims, to be considered enabling.

**Claims 14 and 51** are specifically directed to methods of treating and/or preventing a disease caused by the phosphorylation of c-Jun by JNK3, possibly through inhibition of JNK3 expression or function by BAML1, BPL1 or a peptide comprising the amino acid sequence of SEQ ID No: 1. As described in the previous written description rejection, the specification does not describe representative species of diseases that can be treated by the instant claims so the invention cannot be performed throughout its full scope without undue experimentation.

To prevent a pathological condition means to keep this condition from occurring. Using manic-depressive psychosis, a disease contemplated in the specification as caused the phosphorylation of c-Jun by JNK3, as an example, to prevent manic-depressive psychosis means to keep it from occurring in a subject now or in the future. It is well-known in the art (see for example, the NIMH publication "Bipolar Disorder"), however, that bipolar disorder, the illness leading to manic depressive psychosis, does not have a single cause, but instead is caused by many factors working together.

Although the specification describes how the interaction of BMAL1 and CLOCK is inhibited by the phosphorylation of BMAL1 by JNK3, the prior art does not teach the particular events related to disruption of the circadian rhythm that cause a manic-depressive psychosis. Based on this lack of knowledge and a reasonable interpretation of prevention, one of skill in the art would conclude that no method known currently will

prevent from happening in a subject, now or at any future time, manic depressive psychosis caused by a circadian rhythm disorder.

The specification describes *in vitro* examples of the phosphorylation of BMAL1 by JNK3 and that the use of a partial peptide of JIP1 and JSAP1 will inhibit this phosphorylation. The specification provides no examples of administration of inhibitors of JNK3 to any organism for any purpose and does not provide any specific guidance of how to use compounds that interfere with the expression or function of JNK3 to prevent any disease.

Because no specific method of preventing manic depressive psychosis or any other disease caused by the phosphorylation of c-Jun by JNK3 (which may cause, circadian rhythm disorder) is disclosed in the specification, the skilled artisan would have to perform a large and undue quantity of trial and error experimentation in order to determine how to prevent any disorder related to phosphorylation of c-Jun by JNK3 (which may cause, circadian rhythm disorder) using compounds that interfere with the expression or function of JNK3. In addition, to practice the instant invention, the skilled artisan would be required to monitor any subject for the remainder of their lifetime to ensure that the inhibitor of the invention indeed prevented manic depressive psychosis from happening in said subject. In this case, the quantity of trial and error experimentation required to determine that a method would actually prevent manic-depressive psychosis and the lack of guidance in the specification regarding the direction in which the experimentation should proceed demonstrate that the instant invention is not enabled.

Some embodiments of the claims encompass the use of nucleic acid inhibitors such as antisense oligonucleotides. Therapeutic use of nucleic acids presents unique difficulties that were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). These include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

"Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides no examples of use of any type of inhibitor of JNK3 expression or function in an organism. Given the teachings of Opalinska, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration

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and remaining for a sufficient time to provide successful inhibition of expression of a target gene.

Thus, in order to practice the claimed invention throughout its full scope, the skilled artisan would have to perform undue experimentation to identify what diseases are caused by the phosphorylation of c-Jun by JNK3 (which may cause, circadian rhythm disorders), how to prevent such disorders from occurring throughout the lifetime of an individual and how to predictably deliver some classes of inhibitors to the treated individual. Therefore, **claims 14 and 51** are not enabled for prevention of diseases caused by the phosphorylation of c-Jun by JNK3.

**Claims 14 and 51** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In **claims 14 and 51** applicants have stated that the method of the invention comprises preventing or treating disease(s) caused by the phosphorylation of c-June by JNK3; however applicants have not described or explained as to what these diseases are supposed to be. Furthermore the applicants have stated in **claims 14 and 15** that the claimed method of the invention comprises utilizing one or more polynucleotides that encode a peptide comprising the amino acid of SEQ ID NO:1 but applicants have not explained how the said polynucleotides are intended to be used. For example, are they being administered to a subject?

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In **claims 14 and 51**, BMAL1 needs to be spelled out in the first instance of use. BMAL1 has been cited in the art as being an abbreviation for "Brain and Muscle Arnt-like Protein 1".

In **claims 14 and 51**, BPL1 needs to be spelled out in the first instance of use. BPL has been cited in the art as being an abbreviation for "biotin:protein ligase 1".

Furthermore in **claims 14 and 51** applicants have used the phrase "a homology of 70% to ..."; however applicants are reminded that the concept of "percent homology" is repugnant to the art. Two proteins are either homologous or not, meaning that two proteins either have a common ancestral protein or they do not. A more accurate attempt of comparing protein primary structures (amino acid sequences) is to use "percent identity", as in, a protein having 70% identity to the amino acid sequence of SEQ ID NO: 1.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 14 and 51** are rejected under 35 U.S.C. 102(b) as being anticipated by Ikeda et al., 1997.

Ikeda et al. disclose nucleic acid sequences that encode BMAL1 and its variants that can be used to inhibit the phosphorylation of c-Jun by JNK3 (Figure 2, page 260).

Applicants are reminded that where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties the alloys had or who discovered the properties because the composition is the same and thus must necessarily exhibit the properties.).

See also *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971) (Claim 1 was directed to a parachute canopy having concentric circumferential panels radially separated from each other by radially extending tie lines. The panels were separated "such that the critical velocity of each successively larger panel will be less than the critical velocity of the previous panel, whereby said parachute will sequentially open and thus gradually decelerate." The court found that the claim was anticipated by Menget. Menget taught a parachute having three circumferential panels separated by tie lines. The court upheld the rejection finding that applicant had failed to show that Menget did not possess the functional characteristics of the claims.); *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) (A patent to a pencil for cleaning fingernails was held invalid because a pencil of the same structure for writing was found in the prior art.).

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures

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sufficed to support a *prima facie* case of unpatentability of Spada's polymer latexes for lack of novelty.").

Thus Ikeda et al. teach all the elements of **claims 14 and 51** and these claims are anticipated under 35 USC 102(b).

**Claims 14 and 51** are rejected under 35 U.S.C. 102(b) as being anticipated by EP1130094.

EP1130094 discloses nucleic acid sequences that encode peptide variants that are at least 70% identical to a peptide comprising the amino acid sequence of SEQ ID NO: 1 that can be used to inhibit the phosphorylation of c-Jun by JNK3 (see STIC sequence alignment analysis attached to the instant Office Action and cited in PTO-892).

Applicants are reminded that where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties the alloys had or who discovered the properties because the composition is the same and thus must necessarily exhibit the properties.).

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Thus EP1130094 teaches all the elements of **claims 14 and 51** and these claims are anticipated under 35 USC 102(b).

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert B Mondesi  
Examiner  
Art Unit 1652

*Robert B. Mondesi*  
07-02-2007